

ACUTE KIDNEY INJURY IN CHILDREN WITH *PLASMODIUM FALCIPARUM* MALARIA: DETERMINANTS FOR MORTALITY

Rajniti Prasad, Om P. Mishra

Division of Pediatric Nephrology, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, India

◆ **Background:** Acute kidney injury (AKI) in *P. falciparum* malaria infection is an important morbidity in children. The purpose of the present study was done to observe the renal involvement, associated morbidities and outcome.

◆ **Methods:** Out of 156 patients with severe *P. falciparum* malaria, diagnosed on the basis of compatible clinical presentations and positive malarial parasites in the peripheral blood smear and/or histidine rich protein 2 antigen, 31 had AKI at presentation and were analyzed.

◆ **Results:** Of 31 (19.9%) patients with AKI, 4 were classified at risk, 11 injury, and 16 failure stage, as per pRIFLE criteria (pediatric version of RIFLE [R = risk, I = injury, F = failure, L = loss E = end-stage kidney disease]). Mean age of children with AKI was 7.7 ± 3.2 years. A significantly higher proportion of patients with AKI had hypoglycemia (41.9%), pulmonary edema (32.2%), and disseminated intravascular coagulation (DIC) (29.0%) compared to those without AKI (18.4%, 4.8%, and 3.2%, respectively). Twelve patients (38.7%) required peritoneal dialysis (PD), 8 (25.8%) died, and all were in failure stage. The non-survivors had significantly higher blood urea ($p = 0.005$) and serum creatinine levels ($p = 0.042$), lower glomerular filtration rate ($p < 0.001$), longer duration of illness ($p = 0.003$), and oliguria/anuria ($p = 0.001$) than survivors at admission. On logistic regression analysis, the disseminated intravascular coagulation (DIC), jaundice and parasite density ($\geq 3+$) were found to be significant factors contributing to mortality in children with AKI.

◆ **Conclusions:** Acute kidney injury in *falciparum* malaria is one of the severe systemic complications. Duration of illness and presence of comorbidities adversely affected the outcome.

most severe complications of malaria. As per World Health Organization (WHO) criteria, acute renal failure (serum creatinine level ≥ 3 mg/dL) occurs as a complication of *Plasmodium falciparum* malaria in less than 1–5% of cases (3, 4). The clinically significant renal involvement ranges from asymptomatic urinary abnormalities and mild electrolyte disturbances to AKI. It may present as a component of multi-organ dysfunction or a lone complication (5). Several pathogenic mechanisms interplay for the clinical manifestations. The predominant lesions are acute tubular necrosis resulting from hypovolemia, peripheral pooling of blood, blockage of microcirculation by parasitized red blood cells, interstitial nephritis, immune-mediated proliferative glomerulonephropathy (5, 6) or thrombotic microangiopathy (7).

The management of malaria-induced AKI includes appropriate antimalarial medication, fluid and electrolytes correction, and renal replacement therapy, if required (2, 6). The mortality rate varies from 15–45% (6, 8–10). Mishra *et al.* (11) reported in adult patients that mortality in malaria further increased if there was associated acute renal failure. Using RIFLE criteria to classify AKI in malaria in adults has been reported earlier (12). However, there is a paucity of data regarding assessment of AKI in children suffering from malaria based on pRIFLE classification as well as factors contributing to mortality. We present a single-center analysis of AKI in children with *P. falciparum* malaria in regard to its clinical presentation and determinants of mortality.

PATIENTS AND METHODS

The present study was carried out at a tertiary-care center of a teaching hospital in the Division of Pediatric Nephrology from February 2010 to December 2013. Children aged 2–14 years presenting with fever, satisfying the WHO clinical and laboratory criteria of severe malaria (4) and positive peripheral blood smear and/or histidine rich protein 2 (HRP 2) antigen test were included. The study protocol was approved by the Institute Ethics Committee and informed consent was taken from parents or authorized representatives of each patient.

A detailed history and clinical examination were recorded for each patient. A total of 178 patients with severe malaria presenting consecutively to our hospital during the study period were screened, and of these, 22 cases were excluded

Perit Dial Int 2016; 36(2):213–217 epub ahead of print: 01 Oct 2015
<http://dx.doi.org/10.3747/pdi.2014.00254>

KEY WORDS: AKI; *falciparum* malaria; mortality.

Southeast Asia has contributed about 2.5 million cases to the global burden of malaria, and India alone had 76% of the total cases (1). The proportion of *P. falciparum* malaria is between 10–30% in India and has significant morbidity and mortality (2). Acute kidney injury (AKI) is one of the

Correspondence to: Om P. Mishra, Division of Pediatric Nephrology, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, India.

opmpedia@yahoo.co.uk

Received 3 October 2014; accepted 3 May 2015.

from the study in view of concomitant other infections (enteric fever: 12, septicemia: 4, viral hepatitis: 4, bacterial meningitis: 2). Of the remaining 156 children, 31 cases satisfied the criteria of AKI, classified as per pRIFLE (pediatric version of RIFLE [R = risk, I = injury, F = failure, L = loss E = end-stage kidney disease]) criteria (13) based on percent reduction in estimated glomerular filtration rate taking baseline as 100 mL/1.73m²/min.

A complete hemogram, peripheral blood smear (thick and thin), parasite density, blood urea, serum creatinine, sodium, potassium, bilirubin, arterial blood gases, electrocardiogram and chest X-ray were done for every patient. Urinalysis and cultures were performed on the patients who passed urine. The prothrombin time, activated partial thromboplastin time (APTT), blood culture and ultrasonography of kidney, ureter and bladder were done for all the patients with AKI to exclude disseminated intravascular coagulation (DIC), bacterial infections and pre-existing structural malformations, respectively.

The comorbidities were defined as per WHO criteria (4) such as coma (Glasgow coma scale ≤ 10), convulsions (≥ 2 episodes within 24 h), anemia (hemoglobin < 11 g/dL in 2 – 6 years and < 12 g/dL in 6 – 14 years age group), jaundice (serum bilirubin ≥ 3 mg/dL), hypoglycemia (blood sugar < 40 mg/dL), shock (systolic blood pressure $< 70 + 2 \times \text{age [yr]}$ mmHg), pulmonary edema (presence of respiratory distress and specific chest roentgenographic appearance) and DIC (bleeding manifestations and deranged prothrombin time and APTT).

All the patients were treated with intravenous artesunate (2.4 mg/kg stat dose, then at 12 h, 24 h, and thereafter once daily) and clindamycin (10 mg/kg dose twice daily) for a total

of 7 days as per WHO protocol. Supportive therapy was administered as indicated (4). Patients having AKI were managed with our standard hospital protocol (including management of fluid and electrolyte disturbances, anemia, and hypertension) and peritoneal dialysis (PD) where clinical and biochemical indications existed. None of the patients required mechanical ventilation. During the hospital stay, the patients were monitored for resolution of fever and improvement in urine output, jaundice, shock, DIC, and renal function (blood urea, serum creatinine, sodium, and potassium levels).

STATISTICAL ANALYSIS

The data were analyzed using SPSS version 16 (IBM SPSS Statistics, Chicago, IL, USA). Student's *t*-test was applied to compare the data following Gaussian distribution and Mann-Whitney U test for non-Gaussian distribution. Fisher's exact test was used to compare the proportions, and step-wise logistic regression analysis was done to find out the effect of comorbidities. A *p* value of less than 0.05 was considered significant.

RESULTS

Thirty-one patients (19.9%) had deranged renal functions; 20 cases had oliguria (urine output < 1 mL/kg/h), 6 had anuria, and the other 5 had normal urine output. Four patients were at risk, 11 injury, and 16 in failure stage. There were 20 males. The basic clinical profiles of patients are presented in Table 1. The mean age, duration of illness, and

TABLE 1
Clinical Profile of Children with Severe *P. falciparum* Malaria

Parameters	AKI (n=31)	Non-AKI (n=125)	P value
Age (yrs)	7.7 \pm 3.2	7.3 \pm 2.6	0.47 ^a
Duration of illness (days)	6.1 \pm 1.6	5.8 \pm 1.7	0.38 ^a
Fever (temperature $\geq 99^\circ\text{F}$)	31 (100)	125 (100)	—
Heart rate (per/min)	111 \pm 4.5	116 \pm 5.8	$< 0.001^a$
Respiratory rate (per/min)	28 \pm 4.8	24 \pm 5.7	0.004 ^a
Systolic BP (mmHg)	106 \pm 8.5	112 \pm 6.4	0.001 ^a
Diastolic BP (mmHg)	74 \pm 5.9	68 \pm 4.8	0.001 ^a
Anemia	28 (90.3%)	112 (89.6%)	0.90 ^b
Jaundice	12 (38.7%)	31 (24.8%)	0.12 ^b
Convulsions	11 (35.5%)	33 (26.4%)	0.31 ^b
Pulmonary edema	10 (32.2%)	6 (4.8%)	$< 0.001^b$
Coma	9 (29.0%)	21 (16.8%)	0.12 ^b
DIC	9 (29.0%)	4 (3.2%)	$< 0.001^b$
Shock	7 (25.8%)	13 (10.4%)	0.07 ^b
Hypoglycemia	13 (41.9%)	23 (18.4%)	$< 0.05^b$
Glomerular filtration rate (mL/1.73m ² /min)	17.3 (13.5, 28.1)	103.2 (98.2, 108.8)	$< 0.001^c$

AKI = acute kidney injury; BP = blood pressure; DIC = disseminated intravascular coagulation.

^a Student's *t*-test.

^b Fisher's exact test.

^c Mann-Whitney U test.

cases with anemia, jaundice, convulsions, coma and shock were comparable between patients with and without AKI. Children with AKI had significantly higher respiratory rate, diastolic blood pressure and lower heart rate, systolic blood pressure and glomerular filtration rate than those without AKI. A significantly higher proportion of patients with AKI had pulmonary edema, DIC, and hypoglycemia compared to those having no AKI. None of the patients with AKI had black water fever at presentation.

At presentation, the mean hemoglobin and serum sodium concentrations were lower, while blood urea, serum creatinine,

potassium, and bilirubin levels were significantly higher in children who had AKI as compared to those without AKI (Table 2).

Twelve children (injury: 1, failure: 11) required PD with a mean of 48 ± 20 cycles. Eight cases (25.8%) with AKI died and all belonged to failure stage. The comparison of parameters between survivors and non-survivors is presented in Table 3. The mean blood urea and serum creatinine levels were significantly higher, glomerular filtration rate was lower, and duration of illness and oliguria/anuria were longer at presentation in non-survivors than survivors. A significantly

TABLE 2
Laboratory Parameters in Children with *P. falciparum* malaria (mean \pm SD)

Parameters	AKI children <i>n</i> =31	Non-AKI children <i>n</i> =125	<i>P</i> value
Hemoglobin (g/dL)	5.6 \pm 1.8	6.4 \pm 2.3	0.020 ^a
Total leucocyte counts (/mm ³)	14,426.4 \pm 3,256.4	13,638.4 \pm 28,000.6	0.889 ^a
Polymorphs (%)	73.2 \pm 8.6	68.4 \pm 4.3	0.997 ^a
Platelets count (/mm ³)	91,258 \pm 85,400	98,462 \pm 39,804	0.568 ^b
Blood pH	7.2 \pm 0.1	7.3 \pm 0.12	1.00 ^a
Blood urea (mg/dL)	132.6 \pm 40.4	22.8 \pm 8.6	<0.001 ^a
Serum creatinine (mg/dL)	3.9 \pm 1.9	0.6 \pm 0.12	<0.001 ^a
Serum sodium (mmol/L)	131.3 \pm 5.8	134.7 \pm 4.2	0.002 ^a
Serum potassium (mmol/L)	5.6 \pm 0.7	3.8 \pm 0.8	<0.001 ^a
Serum bilirubin (mg/dL)	4.8 \pm 0.8	2.6 \pm 0.7	<0.001 ^a

SD = standard deviation; AKI = acute kidney injury.

^a Student's *t*-test.

^b Mann-Whitney U test.

TABLE 3
Comparison of Parameters Between Survivors and Non-Survivors in Children with AKI

Parameters	Survivors <i>n</i> =23	Non-survivors <i>n</i> =8	<i>P</i> value
Age (yrs)	7.9 \pm 2.9	7.2 \pm 4.1	0.57 ^b
Duration of illness (days)	5.6 \pm 1.1	7.5 \pm 2.07	0.003 ^a
Duration of oliguria/anuria (days)	1.8 \pm 0.5	3.4 \pm 0.4	0.001 ^a
Hemoglobin (g/dL)	5.7 \pm 1.9	5.5 \pm 1.9	0.84 ^a
Total leucocyte count (/mm ³)	8,750 \pm 1,526.7	8,602.50 \pm 5,445.8	0.91 ^b
Platelets count (/mm ³)	1,05,434.7 \pm 94,368	50,500 \pm 2,635.1	0.12 ^b
Parasite density			
1–2+	19 (82.6%)	0 (0%)	<0.001 ^c
\geq 3+	4 (17.4%)	8 (100%)	
Blood pH	7.2 \pm 0.10	7.2 \pm 0.10	0.60 ^a
Blood urea (mg/dL)	121.1 \pm 36.5	165.7 \pm 33.7	0.005 ^a
Serum creatinine (mg/dL)	3.5 \pm 1.9	4.8 \pm 1.6	0.042 ^a
Serum sodium (mmol/L)	132.1 \pm 6.1	129.0 \pm 4.2	0.19 ^a
Serum potassium (mmol/L)	5.1 \pm 0.6	5.8 \pm 0.7	0.993
Glomerular filtration rate (mL/1.73m ² /min)	18.3 (14.3,49.0)	13.8 (9.8, 17.0)	0.038

AKI = acute kidney injury.

^a Student's *t*-test.

^b Mann-Whitney U test.

^c Fisher's exact test.

TABLE 4
Correlation of Comorbidities with Outcome of Children with AKI

Morbidities	Survivors (n=23)	Non-survivors (n=8)	Fisher's exact test	Odds ratio	95% CI
Pulmonary edema			0.074	6.0	1.13–31.8
Present	5 (50.0%)	5 (50.0%)			
Absent	18 (85.7%)	3 (14.3%)			
DIC			<0.001	73.5	6.85–707.9
Present	2 (22.2%)	7 (77.8%)			
Absent	21 (95.5%)	1 (4.5%)			
Coma			<0.001	73.5	6.85–707.9
Present	2 (22.2%)	7 (77.8%)			
Absent	21 (95.4%)	1 (4.6%)			
Jaundice			<0.01	25.2	3.03–188.8
Present	5 (41.7%)	7 (58.3%)			
Absent	18 (94.7%)	1 (5.3%)			

AKI = acute kidney injury; CI = confidence interval; DIC = disseminated intravascular coagulation.

TABLE 5
Logistic Regression Analysis of Comorbidities and Outcome in Children with AKI

Steps	Comorbidities	Regression coefficient	Regression constant	P value	R ²
Step 1	DIC	4.97	-3.045	<0.001	0.64
Step 2	DIC	21.03	-39.57	<0.01	0.92
	Parasite density	38.19		<0.001	
Step 3	DIC	35.43	-88.64	0.025	1.00
	Parasite density	70.45		<0.001	
	Jaundice	35.64		0.025	

AKI = acute kidney injury; DIC = disseminated intravascular coagulation.

higher proportion of non-survivors had a parasite density of $\geq 3+$ than survivors. At discharge, survivors had normal renal functions.

A significantly higher proportion of non-survivors had comorbidities such as DIC (odds ratio [OR] 73.5, confidence interval [CI] 6.85 – 707.9), coma (OR 73.5, CI 6.85 – 707.9), and jaundice (OR 25.2, CI 3.03 – 188.8) than those who survived (Table 4). On logistic regression analysis, DIC, parasite density ($\geq 3+$) and jaundice were found to be significant risk factors for adverse outcome in children with AKI (Table 5).

DISCUSSION

The occurrence of AKI in severe *falciparum* malaria is common in Southeast Asia and the Indian subcontinent. The precise mechanism of renal involvement is not clearly known but several hypotheses, including mechanical obstruction by the infected erythrocytes, immune-mediated glomerular pathology, fluid loss, decreased oral intake, and alterations in the renal microcirculation, have been proposed (5,14). In the present study, the incidence of AKI was 19.9%. A relatively higher incidence (35 – 48.6%) has been reported

in other studies (6,15). The longer duration of illness and late presentation at hospital complicated the course. This is evident as patients had raised blood urea and serum creatinine levels and of those requiring PD, the majority were in failure stage at admission.

The proportion of cases with renal failure requiring dialytic support was found to be high (55.5 – 75%) in the previous studies (10,15). Twelve cases (38.7%) needed PD in our study. The mortality was 25.8% despite supportive measures and PD. Reported mortality rate in severe malaria with renal failure ranged between 20.2 and 43.8% (3,10,16,17). The non-survivors had a longer duration of illness, oliguria/anuria, and higher levels of retention markers. The late presentation of patients at a tertiary-care center is the main factor responsible for this phenomenon. Associated morbidities in the form of DIC, jaundice, and high parasite density further complicated the disease and lead to mortality. The parasite clearance time is shorter in older children than in younger ones as the former have a lesser parasite index and drug-like artesunate acts faster (18). The WHO has recommended a uniform dose of artesunate irrespective of age, so it was used in the present study. However, drug metabolism has not been studied in relation to age and this may be a further point of

research. Kapoor and Gupta (10) found oliguria, shock, central nervous system involvement, jaundice, DIC, and acute respiratory distress syndrome as bad prognostic factors in a simple univariate analysis. Duration of oligo-anuria, multi-organ dysfunction, and need for renal replacement therapy contributing to higher mortality have been emphasized in previous reports in adult patients (15,19,20). The cytoadherence of *P. falciparum*-infected red blood cells (IRBCs) to the vascular endothelial cells of different host organs along with rosette formation are considered as important pathogenic mechanisms of severe malaria. The IRBCs preferentially sequester in the deep vascular beds of vital organs, including brain, liver, lung, spleen, intestine, and kidney, affecting the microcirculation (21).

Esezobor *et al.* (22) analyzed the etiology of AKI in children at a tertiary hospital and reported that the need for dialysis itself contributed to mortality. Because of the hypercatabolic state of malarial AKI, hemodialysis or PD should be immediately performed in a situation of rapid increase in creatinine concentration. Although PD is less effective because of the complicating circulatory disturbances, it is often the only dialytic modality available in areas where malaria is endemic. Because of its simplicity and feasibility in developing countries, it can be instituted earlier wherever indicated (23). Attention should be given to comorbidities regarding management as their presence adversely affects the outcome. Moreover, these patients require early referral and timely institution of antimalarial and supportive therapy along with dialytic intervention in order to improve the outcome. The main limitation of the study is small sample size of AKI cases with severe malaria. It was an attempt to find out the significant factors contributing to mortality. However, further prospective study on a larger sample size could better evaluate the prognostic factors in these children.

CONCLUSIONS

Acute kidney injury in *falciparum* malaria is a severe complication and presence of DIC, jaundice, and high parasite density are important contributing factors to mortality. Timely interventions in the form of antimalarial and supportive therapy including dialysis can be life-saving in these children.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

REFERENCES

1. Kondrachine AV. Malaria in southeast Asia region. *Indian J Malariol* 1992; 29:129–80.
2. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. *Nature* 2005; 434:214–7.
3. Prakash J, Singh AK, Gujrati S, Maheshwan A. Acute renal failure in malaria: changing trends. *Indian J Nephrol* 2002; 12:113–7.
4. WHO guidelines for the treatment of malaria, 2nd ed., 2010: 35–47.
5. Barosum RS. Malarial nephropathies. *Nephrol Dial Transplant* 1998; 38:1588–97.
6. Mishra SK, Das BS. Malaria and acute kidney injury. *Semin Nephrol* 2008; 28(4):395–408.
7. Sinha A, Singh G, Bhat AS, Mohapatra S, Gulati A, Hari P, *et al.* Thrombotic microangiopathy and acute kidney injury following vivax malaria. *Clin Exp Nephrol* 2013; 17(1):66–72.
8. Das BS. Renal failure in malaria. *J Vector Borne Dis* 2008; 45:83–97.
9. Barosum RS. Malarial acute renal failure. *J Am Soc Nephrol* 2000; 11:2147–54.
10. Kapoor K, Gupta S. Malarial acute kidney injury in a paediatric intensive care unit. *Trop Doct* 2012; 42(4):203–5.
11. Mishra SK, Mohanty S, Satpathy SK, Mohapatra DN. Cerebral malaria in adults: a description of 526 cases admitted to Ispat General Hospital in Rourkela, India. *Ann Trop Med Parasitol* 2007; 101:187–93.
12. Thanachartwet V, Desakorn V, Sahassananda D, Win K, Yazar KK, Supaporn T. Acute renal failure in patients with severe *falciparum* malaria: using the WHO and RIFLE criteria. *Int J Nephrol* 2013. Article ID 841518.
13. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int* 2007; 71:1028–35.
14. Eiam-Ong S, Sitprija V. *Falciparum* malaria and the kidney: a model of inflammation. *Am J Kidney Dis* 1998; 32:361–75.
15. Panda SK, Das MC, Meher LK, Rathod PK. Risk factors for acute renal failure in severe *falciparum* malaria. *Indian J Nephrol* 2003; 13:55–8.
16. Naqvi R, Ahmad E, Akhtar F, Naqvi A, Rizvi A. Outcome in severe acute renal failure associated with malaria. *Nephrol Dial Transplant* 2003; 18:1820–3.
17. Sheiban AK. Prognosis of malaria associated severe acute renal failure in children. *Renal failure* 1998; 21:63–6.
18. Ndour PA, Lopera-Mesa TM, Diakite SAS, Chiang, S, Mouri O, Roussel C, *et al.* *Plasmodium falciparum* clearance is rapid and pitting independent in immune Malian children treated with artesunate for malaria. *J Infect Dis* 2015; 211:290–7.
19. Mehta KS, Halankar AR, Makwana PD, Torane PP, Satija PS, Shah VB. Severe acute renal failure in malaria. *J Postgrad Med* 2001; 47:24.
20. Mishra SK, Mahanta KC. Peritoneal dialysis in patients with malaria and acute kidney injury. *Perit Dial Int* 2012; 32(6):656–9.
21. Pongponratan E, Riganti M, Punpoowong B, Aikawa M. Microvascular sequestration of parasitized erythrocytes in human *falciparum* malaria: a pathological study. *Am J Trop Med Hyg* 1991; 44:168–75.
22. Esezobor CI, Ladapo TA, Osinaik B, Lesi FE. Paediatric acute kidney injury in a tertiary hospital in Nigeria: prevalence, causes and mortality rate. *PLoS One* 2012; 7(12):e51229.
23. Mishra OP, Gupta AK, Pooniya V, Prasad R, Tiwary NK, Schaefer F. Peritoneal dialysis in children with acute kidney injury: a developing country experience. *Perit Dial Int* 2012; 32:431–6.